Sponsor

Novartis

Generic Drug Name

Canakinumab

Therapeutic Area of Trial

Gouty arthritis

Approved Indication

Canakinumab was first registered for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS) in the United States on 17 Jun 2009. Novartis is currently Marketing Authorization Holder in 69 countries worldwide for the 150 mg powder for solution for injection and in 25 countries worldwide for the 150 mg powder and solvent for injection (convenient kit).

Approval was obtained in the EU on 24 Jan 2013 for the application to extend the treatment in CAPS to children aged two years and older as well as to increase the maximum dose up to 600 mg or 8 mg/kg every 8 weeks in patients who do not achieve a satisfactory clinical response at the currently approved dose. This label extension was also approved in Russia, Philippines and Argentina.

Canakinumab also is approved for the treatment of acute gouty arthritis (GA) attacks in the Philippines Russia, Ecuador, Argentina, Israel, and Mexico. Approval was obtained in EU for the indication of "symptomatic treatment of acute gouty arthritis in patients with frequent attacks (≥ 3 in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDS) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate."

Canakinumab has also been approved for the treatment of systemic juvenile idiopathic arthritis (SJIA) in the Philippines, Russia and the United States. Submissions are either pending or are in progress worldwide.

Protocol Number

CACZ885H2357E3

Title

An open-label extension study of CACZ885H2356E2 and CACZ885H2357E2 on the treatment and prevention of gout flares in patients with frequent flares for whom NSAIDs and/or colchicine are contraindicated, not tolerated or ineffective

Study Phase

Phase III

Study Start/End Dates

10-Nov-2011 (first patient first visit) to 22-May-2013 (last patient last visit)

Study Design/Methodology

This was an 18-month, multi-center, open-label, clinical extension study. Patients completing earlier second extension studies (CACZ885H2356E2 and CACZ885H2357E2) continued to be treated in this combined extension 3 study for any new gouty arthritis flare on demand with one subcutaneous (s.c.) injection of canakinumab 150 mg.

Centers

Total of 60 centers in this extension study: Australia (1), Canada (4), Estonia (2), Germany (3), Latvia (1), Lithuania (5), Russia (7), Switzerland (1), Ukraine (2), United States (34).

Objectives

The primary objective of this study was to assess the long-term safety and tolerability of canakinumab, particularly with regards to potential consequences of immunosuppression (e.g. serious infections or malignancies) and immunogenicity after multiple treatments.

Secondary objectives included 1) to evaluate the long-term efficacy of canakinumab, defined as frequency of new flares, patient's assessment of gout pain intensity (Likert scale) over time, patient's global assessment of response to treatment (Likert scale) over time; 2) to evaluate the efficacy of canakinumab with regards to inflammatory markers (high sensitivity C-reactive protein [hsCRP]); 3) to evaluate the immunogenicity of canakinumab; and 4) to evaluate the safety in the concomitant use of canakinumab with different urate lowering therapy regimens.

Test Product (s), Dose(s), and Mode(s) of Administration

All patients were to receive canakinumab 150 mg s.c. administered as PFS (Pre Filled Syringes), given on demand upon new flares. Canakinumab PFS for s.c. injection were supplied to the investigators at dose strengths of 150 mg canakinumab in 1 mL solution.

Statistical Methods

The data analysis was cumulative follow-up analysis including all the data from the core (CACZ885H2356 and H2357) and all of the extension studies.

For demographic and baseline characteristics (from the core study), summary statistics are newly provided for the ULT subset of patients initiating or modifying ULT during the conduct of this extension 3 study.

The safety set was used for the analysis of safety data during the core and extension studies. Adverse events (AE) and serious adverse events are summarized by presenting, for each treatment group, the incidence rate adjusted for the time of exposure (per 100 patient years) for occurrence of each primary system organ class and preferred term. All other information collected (e.g. severity, relationship to study drug) was tabulated and listed as appropriate. In addition, AE (including infections, serious infections or malignancies) were coded using the MedDRA dictionary that provided the primary system organ class and preferred term information. A dot-plot of all AEs over time is provided for canakinumab 150 mg s.c. patients who were re-treated and for triamcinolone acetonide 40 mg i.m. patients who were treated with canakinumab were provided.

All efficacy analyses were performed using the FAS or the MAS. Summary statistics is provided for the flare rate per year by treatment using the MAS. Flare rate per year is calculated as the number of new gout flares over the period of observation in years. Patient's assessment of gout pain intensity (Likert scale), global assessment of response to treatment (Likert scale) is presented with frequency tables by treatment for all patients and for patients who were re-treated using the MAS. Summary statistics is provided for hsCRP presenting absolute values and changes from baseline using the MAS.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients, who completed the 2nd extension studies CACZ885H2356E2 and CACZ885H2357E2 up to and including the End of Study visit (Visit14) having fulfilled the entry criteria, were eligible for this third extension study.

Patients were excluded from this extension study if their entry was considered inappropriate by the treating physician.

Participant Flow

Patient disposition by treatment (Randomized Set)

	ACZ885 150mg sc (N=227)		Triam 40mg im (N=229)		
	All ACZ N=227	Re-treated with ACZ N=136	All Triam N=229	Treated with ACZ N=83	Total N=456
	n (%)	n (%)	n (%)	n (%)	n (%)
Completed core studies	208 (91.6)	136 (100.0)	208 (90.8)	83 (100.0)	416 (91.2)
Discontinued core studies	19 (8.4)	0 (0.0)	21 (9.2)	0 (0.0)	40 (8.8)
Entered extension 1 studies	174 (76.7)	129 (94.9)	161 (70.3)	83 (100.0)	335 (73.5)
Completed extension 1 studies	165 (72.7)	128 (94.1)	152 (66.4)	83 (100.0)	317 (69.5)
Discontinued extension 1 studies	9 (4.0)	1 (0.7)	9 (3.9)	0 (0.0)	18 (3.9)
Entered extension 2 studies	141 (62.1)	120 (88.2)	131 (57.2)	83 (100.0)	272 (59.6)
Completed extension 2 studies	132 (58.1)	113 (83.1)	117 (51.1)	78 (94.0)	249 (54.6)
Discontinued extension 2 studies	9 (4.0)	7 (5.1)	14 (6.1)	5 (6.0)	23 (5.0)
Entered extension 3 study	87 (38.3)	82 (60.3)	49 (21.4)	49 (59.0)	136 (29.8)
Completed extension 3 study	79 (34.8)	74 (54.4)	43 (18.8)	43 (51.8)	122 (26.8)
Discontinued extension 3 study	8 (3.5)	8 (5.9)	6 (2.6)	6 (7.2)	14 (3.1)
Discontinued core, extension 1, extension 2, or extension 3 study	45 (19.8)	16 (11.8)	50 (21.8)	11 (13.3)	95 (20.8)
Reason for discontinuation					
Adverse event(s)	2 (0.9)	1 (0.7)	5 (2.2)	5 (6.0)	7 (1.5)
Abnormal laboratory value(s)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	6 (2.6)	0 (0.0)	6 (1.3)
Patient's condition no longer requires study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient withdrew consent	19 (8.4)	7 (5.1)	17 (7.4)	2 (2.4)	36 (7.9)
Lost to follow-up	18 (7.9)	7 (5.1)	13 (5.7)	2 (2.4)	31 (6.8)
Administrative problems	2 (0.9)	0 (0.0)	4 (1.7)	2 (2.4)	6 (1.3)
Death	2 (0.9)	1 (0.7)	2 (0.9)	0 (0.0)	4 (0.9)
Protocol deviation	1 (0.4)	0 (0.0)	2 (0.9)	0 (0.0)	3 (0.7)

The primary reason for discontinuation as given by the investigator on the study completion eCRF was summarized.

The data are presented according to the original treatment the patients were randomized to.

If patient was randomized to Triam 40mg im and discontinued after switching to ACZ 150mg sc, this discontinuation is shown in both 'All Triam' and 'Treated with ACZ' columns.

Analysis sets by treatment (Randomized Set)

	ACZ885 150mg sc (N=227)		Triam 40mg im (N=229)		
	All ACZ N=227	Re-treated with ACZ N=136	All Triam N=229	Treated with ACZ N=83	Total N=456
	n (%)	n (%)	n (%)	n (%)	n (%)
Randomized Set	227 (100.0)	136 (100.0)	229 (100.0)	83 (100.0)	456 (100.0)
Full Analysis Set	225 (99.1)	136 (100.0)	229 (100.0)	83 (100.0)	454 (99.6)
Modified Analysis Set	225 (99.1)	136 (100.0)	229 (100.0)	83 (100.0)	454 (99.6)
Safety Set	225 (99.1)	136 (100.0)	229 (100.0)	83 (100.0)	454 (99.6)
ULT optimization Subset1	29 (12.8)	29 (21.3)	11 (4.8)	11 (13.3)	40 (8.8)
ULT optimization Subset2	52 (22.9)	47 (34.6)	25 (10.9)	16 (19.3)	77 (16.9)

ULT optimization Subset1: Patients initiating or modifying ULT during the conduct of the extension 3 study.
ULT optimization Subset2: Patients initiating or modifying ULT during the conduct of core, E1, E2 or E3 studies.

Baseline Characteristics

Demographic and background characteristics by treatment (Safety Set)

Baseline demographic, background, and disease characteristics were reported in the core, first and second extension studies (CACZ885H2356E1, CACZ885H2356E2, CACZ885H2357E1 and CACZ885H2357E2), and were generally comparable for the two treatment groups. The majority of patients were Caucasian and male.

As the demographic and other baseline characteristics (safety set) for this third extension study was expected to mirror those already reported in the Extension 2 Clinical Study Reports, they have not been included again in this combined third extension report.

Outcome Measures

Primary Outcome Result(s)

As the primary objective of this extension study was to evaluate the long-term safety, tolerability and immunogenicity of canakinumab 150 mg s.c. administered as PFS, there is no primary efficacy variable. All efficacy variables are part of the secondary objectives of the study.

Secondary Outcome Result(s)

Flare rate per year: Summary statistics by treatment (Modified Analysis Set)

	ACZ885 150mg sc (N=225)		Triam 40mg im (N=229)	
Statistic	All ACZ N=225	Re-treated With ACZ N=136	All Triam N=229	Treated with ACZ N=83
N	225	136	229	83
Mean	1.109	1.689	2.459	0.996
SD	1.608	1.627	3.701	1.094
Min	0.00	0.33	0.00	0.00
Q1	0.000	0.700	0.000	0.000
Median	0.676	1.310	1.255	0.846
Q3	1.467	2.144	3.765	1.627
Max	12.89	12.89	28.10	5.67

Flare rate is calculated as the number of new flares over the period of observation in years.
Data for flares on Triam 40mg im are presented in 'All Triam' column; data for flares on ACZ885 150mg sc are presented in all other columns.

Flare rate per year: Summary statistics by treatment (ULT optimization Subset1)

	ACZ885 150mg sc (N=29)		Triam 40mg im (N=11)	
	All ACZ	Re-treated with ACZ	All Triam	Treated with ACZ
Statistic	**N=29**	**N=29**	**N=11**	**N=11**
N	29	29	11	11
Mean	1.361	1.361	5.787	2.101
SD	0.688	0.688	4.436	1.365
Min	0.66	0.66	2.14	0.82
Q1	0.686	0.686	3.708	1.320
Median	1.018	1.018	4.401	1.725
Q3	1.705	1.705	5.398	2.400
Max	3.38	3.38	17.19	5.67

Flare rate is calculated as the number of new flares over the period of observation in years.
Data for flares on Triam 40mg im are presented in 'All Triam' column; data for flares on ACZ885 150mg sc are presented in all other columns.

Post-baseline flares compared to baseline flare: clinical response in patients who were re-treated with ACZ (Modified Analysis Set)

	ACZ885 150mg sc re-treated with ACZ (N=136)		Triam 40mg im treated with ACZ (N=83)	
Assessment / Timepoint	**Baseline flare**	**Last new flare**	**1st new flare on ACZ**	**Last new flare**
Pain intensity (Likert scale): None or Mild				
Baseline	1 / 135 (0.7)	4 / 135 (3.0)	3 / 83 (3.6)	3 / 83 (3.6)
24 hours post-dose	67 / 128 (52.3)	41 / 128 (32.0)	38 / 80 (47.5)	22 / 80 (27.5)
48 hours post-dose	83 / 124 (66.9)	54 / 124 (43.5)	58 / 80 (72.5)	41 / 80 (51.3)
72 hours post-dose	94 / 130 (72.3)	74 / 130 (56.9)	67 / 80 (83.8)	59 / 80 (73.8)
4 days post-dose	96 / 128 (75.0)	86 / 128 (67.2)	70 / 80 (87.5)	65 / 80 (81.3)
5 days post-dose	100 / 129 (77.5)	93 / 129 (72.1)	71 / 80 (88.8)	64 / 80 (80.0)
6 days post-dose	95 / 127 (74.8)	95 / 127 (74.8)	71 / 79 (89.9)	67 / 79 (84.8)
7 days post-dose	102 / 127 (80.3)	104 / 127 (81.9)	72 / 78 (92.3)	69 / 78 (88.5)
Patient's global assessment of response to treatment: Excellent or Good				
72 hours post-dose	81 / 127 (63.8)	64 / 127 (50.4)	51 / 74 (68.9)	46 / 74 (62.2)
7 days post-dose	**96 / 128 (75.0)**	**86 / 128 (67.2)**	**65 / 78 (83.3)**	**62 / 78 (79.5)**

At each timepoint only patients with a value at both baseline flare and the post-baseline flare are included.

Safety Results

Exposure adjusted (per 100 patient years) incidence of frequent AEs (> 5 in any treatment group) by primary system organ class (Safety Set)

	ACZ885 150mg sc (N=225)			Triam 40mg im (N=229)		
		Re-treated with ACZ N=136			Treated with ACZ N=83	
	All ACZ N=225	Before (1)	After (1)	All Triam N=229	Before (1)	After (1)
	n (IR/ 100 pyr)	n (IR/ 100 pyr)	n (IR/ 100 pyr)	n (IR/ 100 pyr)	n (IR/ 100 pyr)	n (IR/ 100 pyr)
Total	935 (264.6)	307 (388.8)	450 (205.8)	472 (308.8)	182 (296.0)	222 (175.0)
Musculoskeletal and connective tissue disorders	147 (41.6)	36 (45.6)	78 (35.7)	66 (43.2)	30 (48.8)	26 (20.5)
Investigations	126 (35.7)	48 (60.8)	61 (27.9)	72 (47.1)	19 (30.9)	21 (16.6)
Infections and infestations	134 (37.9)	47 (59.5)	67 (30.6)	56 (36.6)	24 (39.0)	33 (26.0)
Metabolism and nutrition disorders	70 (19.8)	23 (29.1)	37 (16.9)	33 (21.6)	12 (19.5)	22 (17.3)
Nervous system disorders	62 (17.5)	19 (24.1)	26 (11.9)	37 (24.2)	16 (26.0)	13 (10.2)
Gastrointestinal disorders	56 (15.8)	19 (24.1)	22 (10.1)	38 (24.9)	13 (21.1)	25 (19.7)
Vascular disorders	53 (15.0)	14 (17.7)	29 (13.3)	24 (15.7)	10 (16.3)	9 (7.1)
Renal and urinary disorders	40 (11.3)	12 (15.2)	21 (9.6)	16 (10.5)	6 (9.8)	9 (7.1)
Cardiac disorders	28 (7.9)	8 (10.1)	13 (5.9)	25 (16.4)	6 (9.8)	10 (7.9)
Injury, poisoning and procedural complications	31 (8.8)	11 (13.9)	15 (6.9)	21 (13.7)	14 (22.8)	7 (5.5)
General disorders and administration site conditions	33 (9.3)	12 (15.2)	10 (4.6)	15 (9.8)	6 (9.8)	11 (8.7)
Skin and subcutaneous tissue disorders	31 (8.8)	15 (19.0)	14 (6.4)	16 (10.5)	7 (11.4)	5 (3.9)
Respiratory, thoracic and mediastinal disorders	26 (7.4)	6 (7.6)	15 (6.9)	14 (9.2)	5 (8.1)	9 (7.1)
Blood and lymphatic system disorders	25 (7.1)	11 (13.9)	7 (3.2)	4 (2.6)	3 (4.9)	8 (6.3)
Psychiatric disorders	15 (4.2)	6 (7.6)	5 (2.3)	13 (8.5)	3 (4.9)	3 (4.7)

6 (4.7)

Primary system organ classes are sorted by descending frequency of the total number of events observed for all patients.

n = Number of events.

The incidence rate per 100 patient-years (IR/100 pyr) is 100 times (total number of occurrence of events divided by patient-years). It is calculated per SOC level.

Patient-years is the total time at risk in years. It is the sum of all patient's times at risk, i.e. duration of exposure until the date of last study day.

(1) 1st treatment/re-treatment with ACZ.

Exposure adjusted (per 100 patient years) incidence of frequent AEs (> 5 in any treatment group) by preferred term (Safety Set)

	ACZ885 150mg sc (N=225)			Triam 40mg im (N=229)		
		Re-treated with ACZ N=136			Treated with ACZ N=83	
	All ACZ N=225	Before (1)	After (1)	All Triam N=229	Before (1)	After (1)
	n (IR/ 100 pyr)	n (IR/ 100 pyr)	n (IR/ 100 pyr)	n (IR/ 100 pyr)	n (IR/ 100 pyr)	n (IR/ 100 pyr)
Hypertension	42 (11.9)	10 (12.7)	25 (11.4)	20 (13.1)	8 (13.0)	7 (5.5)
Arthralgia	26 (7.4)	5 (6.3)	17 (7.8)	19 (12.4)	7 (11.4)	5 (3.9)
Headache	21 (5.9)	6 (7.6)	6 (2.7)	14 (9.2)	5 (8.1)	2 (1.6)
Upper respiratory tract infection	25 (7.1)	7 (8.9)	16 (7.3)	6 (3.9)	3 (4.9)	5 (3.9)
Back pain	28 (7.9)	6 (7.6)	16 (7.3)	2 (1.3)	1 (1.6)	1 (0.8)
Gout	13 (3.7)	2 (2.5)	10 (4.6)	10 (6.5)	4 (6.5)	5 (3.9)
Osteoarthritis	19 (5.4)	4 (5.1)	9 (4.1)	2 (1.3)	0.0 (0.0)	5 (3.9)
Nasopharyngitis	8 (2.3)	4 (5.1)	2 (0.9)	10 (6.5)	7 (11.4)	7 (5.5)
Pain in extremity	6 (1.7)	2 (2.5)	4 (1.8)	12 (7.8)	7 (11.4)	1 (0.8)
Muscle spasms	5 (1.4)	2 (2.5)	2 (0.9)	11 (7.2)	8 (13.0)	0.0 (0.0)
Influenza	9 (2.5)	1 (1.3)	8 (3.7)	1 (0.7)	0.0 (0.0)	1 (0.8)

Preferred terms are sorted by descending frequency of the total number observed for all patients. n = Number of events.

The incidence rate per 100 patient-years (IR/100 pyr) is 100 times (total number of occurrence of events divided by patient-years).It is calculated per SOC level.

Patient-years is the total time at risk in years. It is the sum of all patient's times at risk, i.e. duration of exposure until the date of last study day.

(1) 1st treatment/re-treatment with ACZ.

Exposure adjusted (per 100 patient years) incidence of deaths, other serious adverse events or related discontinuations (Safety Set)

	ACZ885 150mg sc (N=225)			Triam 40mg im (N=229)		
		Re-treated with ACZ N=136			Treated with ACZ N=83	
	All ACZ N=225	Before (1)	After (1)	All Triam N=229	Before (1)	After (1)
	n (IR/100 pyr)	n (IR/100 pyr)	n (IR/100 pyr)	n (IR/100 pyr)	n (IR/100 pyr)	n (IR/100 pyr)
Any AE(s)	873 (247.0)	285 (360.9)	413 (188.8)	451 (295.0)	161(261.9)	205 (161.6)
Serious AE(s) or related discontinuations						
Death	2 (0.6)	0 (0.0)	1 (0.5)	2 (1.3)	0 (0.0)	0 (0.0)
Non-fatal SAE(s)	59 (16.7)	12 (15.2)	32 (14.6)	25 (16.4)	2 (3.3)	14 (11.0)
Non-fatal SAE(s) leading to discontinuation	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	3 (2.4)
Non-serious AE(s) leading to discontinuation	2 (0.6)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	2 (1.6)

(1) 1st treatment/re-treatment with ACZ; n = Number of events.

The incidence rate per 100 patient-years (IR/100 pyr) is 100 times (total number of occurrence of events divided by patient-years). It is calculated per category. Patient-years is the total time at risk in years. It is the sum of all patient's times at risk, i.e. duration of exposure until the date of last study day.

Other Relevant Findings

None

Date of Clinical Trial Report

12 May 2014

Date Inclusion on Novartis Clinical Trial Results Database

15 May 2014

Date of Latest Update

NA